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GOODWIN PROCTER LLP
135 COMMONWEALTH DRIVE
MENLO PARK, CA 94025

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KEMMERER, ELIZABETH	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/990,436
Filing Date: November 14, 2001
Appellant(s): BOTSTEIN ET AL.

James A. Fox
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 14 April 2008 appealing from the Office action mailed 12 October 2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

U.S. Patent Application Serial No. 09/992,643 is also under appeal. The examiner's answer for that application is being prepared concurrently with the instant examiner's answer.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Pennica, D. et al. "WISP genes are members of the connective tissue growth factor family that are up-regulated in Wnt-1-transformed cells and aberrantly expressed in human colon tumors" Proc. Natl. Acad. Sci., vol95 (December 1998, pp. 14717-14722.

Konopka, J.B. et al. "Variable expression of the translocated c-abl oncogene in Philadelphia-chromosome-positive B-lymphoid cell lines from chronic myelogenous leukemia patients" Proc. Natl. Acad. Sci. USA, vol83 (June 1986), pp. 4049-4052.

Fleischhacker, M. et al. "DNA Aneuploidy in Morphologically Normal Colons from Patients with Colon Cancer" Modern Pathology, vol8, no4 (1995), pp. 360-365.

Godbout, R. et al. "Overexpression of a DEAD box protein (DDX1) in neuroblastoma and retinoblastoma cell lines" J. Biol. Chem. vol273, no. 33 (14 August 1998), pp. 21161-21168.

Hittelman, W. "Genetic Instability in Epithelial Tissues at Risk for Cancer" Ann. NY Acad. Sci., vol952 (2001), pp. 1-12.

Li, R. et al. "Identification of putative oncogenes in lung adenocarcinoma by a comprehensive functional genomic approach" Oncogene vol25 (2006), pp. 2628-2635.

Sen "Aneuploidy and cancer" Curr. Opin. Oncol. vol12 (2000), pp. 82-88.

Hanna, J.S. and Mornin, D. "HER-2/neu Breast Cancer Predictive Testing" Pathology Associates Medical Laboratories (1999), pp. 1-2.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 119-123 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility.

Claims 119-123 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The claims are directed to antibodies that bind the polypeptide of SEQ ID NO: 207. Claims are also presented to various antibody forms, including monoclonal,

humanized, fragment, and labeled antibodies. Whether or not the claimed antibodies have utility and are enabled depends entirely upon whether or not the polypeptide they bind have utility and enablement. The specification discloses the polypeptide of SEQ ID NO: 207, also known as PRO1112. Appellant has gone on record as relying upon the gene amplification assay as providing utility and enablement for the claimed antibodies. See Appeal Brief (received 14 April 2008), p. 4, beginning of arguments.

At pages 539-555 of the specification, Example 170 discloses a gene amplification assay in which genomic DNA encoding PRO1112 had a ΔCt value of at least 1.0 for seven out of fourteen lung tumors and twelve out of fourteen colon tumor samples when compared to a pooled control of blood DNA from several healthy volunteers. Example 170 asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the polypeptides and their antibodies are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer (p. 539, lines 21-24). At page 548, ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." It is noted that at page 548, it is stated that samples are used if their values are within 1 Ct of the 'normal standard'. It is further noted that the ΔCt values at pages 550-554 are expressed (a) with values to one one-hundredth of a unit (e.g. 1.29).

First, there are several problems with the data provided in this example. The art recognizes that lung and colon epithelium is can be aneuploid without the presence of cancer. Specifically, Hittelman (2001, Ann. N. Y. Acad. Sci. 952:1-12) reports that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy **before** the epithelial cells turn cancerous. See especially p. 4, Figure 4. The gene amplification assay in the instant specification does not provide a comparison between the lung tumor samples and normal lung epithelium and does not correct for aneuploidy. Thus it is not clear that PRO1112 is amplified in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium. One skilled in the art would not conclude that PRO1112 is a diagnostic probe for lung cancer unless it is clear that PRO1112 is amplified to a clearly greater extent in true lung tumor tissue relative to non-cancerous lung epithelium. Regarding colon tissue, pre-malignant lesions and ulcerative colitis have been associated with aneuploidy. See Fleischhacker et al. (1995, Modern Pathology 8:360-365), especially p. 360, 1st paragraph of introduction. The gene amplification assay in the instant specification does not provide a comparison between the colon tumor samples and normal colon epithelium and does not correct for aneuploidy. Thus it is not clear that PRO1112 is amplified in cancerous colon epithelium more than in damaged (non-cancerous) colon epithelium. One skilled in the art would not conclude that PRO1112 is a diagnostic probe for colon cancer unless it is clear that PRO1112 is amplified to a clearly greater extent in true colon tumor tissue relative to non-cancerous colon epithelium.

Second, even if the data had been corrected for aneuploidy and a proper control had been used, the data have no bearing on the utility of the claimed PRO1112 *antibodies*. In order for PRO1112 polypeptides to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and increased polypeptide levels. No data regarding PRO1112 mRNA or PRO1112 polypeptide levels in lung or colon tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between genomic DNA levels and polypeptide levels. A specific example of the lack of correlation between genomic DNA amplification and increased mRNA expression is provided by Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." Another specific example is provided by Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract). Yet another specific example is provided by Hanna and Mornin (1999, Pathology Associates Medical Laboratories), wherein diagnosis of breast cancer included testing both the

amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Thus Hanna and Mornin provide evidence of the recognition in the art that the level of polypeptide expression must be tested empirically to determine whether or not the polypeptide can be used as a diagnostic marker for a cancer. The specification does not provide data as to whether or not the polypeptide level of PRO1112 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since the asserted utility for the claimed antibodies is not in currently available form, and further experimentation is *required* to reasonably confirm the asserted real-world use, the asserted utility is not substantial.

The *general* concept of gene amplification's lack of correlation with mRNA/protein overexpression in cancer tissue is addressed by Sen (2000, Curr. Opin. Oncol. 12:82-88). Specifically, Sen teaches that cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes. A slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Aneuploidy is a feature of damaged tissue, and is commonly found in lung and colon tissues, which are subject to environmental influences. Such does not invariably lead to cancer; rather, the development of cancer is rare, as evidenced for example by the fact that the general population is constantly suffering damage to lung cells via air pollution, whereas lung cancer remains relatively rare. The gene amplification assay in the instant specification does not provide a comparison between the lung tumor samples and normal lung epithelium or between colon cancer and normal colon samples, and does not correct for

aneuploidy. Thus it is not clear that PRO1112 gene is amplified in cancerous lung or colon epithelium more than in damaged (non-cancerous) lung or colon epithelium. One skilled in the art would not conclude that the PRO1112 gene is a diagnostic probe for lung cancer or a target for therapeutic drug development unless it is clear that the PRO1112 gene is amplified to a clearly greater extent in true lung tumor and colon tumor tissue relative to non-cancerous lung and colon epithelium. Hittelman (2001, Ann. N. Y. Acad. Sci. 952:1-12) also speaks to this issue. Again, the data in the specification were not corrected for such aneuploidy events.

Furthermore, Godbout et al. (1998, J. Biol. Chem. 273(33):21161-8) teach a general lack of correlation between gene amplification and mRNA/protein overexpression. The abstract of Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. ***Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified***." (emphasis added). The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state ***"It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell*** (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer

and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." (emphasis added). There is no evidence in the instant application that PRO1112 confers any growth advantage to a cell. For example, PRO1112 bears no significant sequence similarity with any previously characterized proteins known to play a role in cell division or cell survival. Thus it cannot be presumed that the PRO1112 polypeptide is overexpressed because the genomic DNA including the gene being studied is amplified.

An additional reference that provides evidence that gene amplification does not generally lead to increased transcript is Li et al. (2006, Oncogene, Vol. 25, pages 2628-2635). Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "***In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels***, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma*." Since more than half of the amplified genes were not

overexpressed, Li et al. constitutes strong evidence that ***it is more likely than not that gene amplification does NOT correlate with increased protein levels***, absent evidence that the protein has biological relevance in cancer. There is no such evidence for PRO1112.

Therefore, data pertaining to PRO1112 genomic DNA do not indicate anything significant regarding the PRO1112 polypeptide that is specifically bound by the claimed antibodies. The data do not support the specification's assertion that PRO1112 polypeptides and their antibodies can be used as cancer diagnostic agents. Significant further research would have been required of the skilled artisan to reasonably confirm that the PRO1112 polypeptide is overexpressed in any cancer to the extent that the polypeptide or antibodies that bind it could be used as cancer diagnostic agents, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO1112 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO1112 **polypeptides and antibodies** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides and antibodies. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful

conclusion."

In view of the preponderance of evidence supporting the rejections (Pennica et al., Konopka et al., Fleischhacker et al., Sen, Hittelman, Godbout et al., and Li et al.), the rejections are properly maintained.

(10) Response to Argument

From p. 4 to p. 5 of the Appeal Brief, Appellant provides a summary of their arguments. Appellant begins by reviewing the data presented in Example 170, which has been analyzed in detail in the rejection above. Specifically, Appellant argues that the skilled artisan would expect that the gene amplification data for PRO1112 gene implicates that the PRO1112 polypeptide is overexpressed. This has been fully considered but is not found to be persuasive because of the evidence that gene amplification is not correlated with polypeptide overexpression (Pennica et al., Konopka et al., Hanna and Mornin, Godbout et al., Li et al., Hittelman, and Sen).

At p. 4 of the Appeal Brief, Appellant refers to the Goddard declaration as evidence that gene amplification indicates the gene is useful as a marker for cancer diagnosis. The Goddard declaration under 37 CFR 1.132 filed 25 June 2004 is insufficient to overcome the rejection of claims 119-123 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action because it does not address the main issue, that is, whether or not gene amplification indicates anything useful about the encoded polypeptide or antibodies that bind it.

At p. 4 of the Brief, Appellant urges that Orntoft et al., Hyman et al., and Pollack et al. constitute evidence that, in general, gene amplification increases mRNA expression. This has been fully considered but is not found to be persuasive. Orntoft et al. could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract). Appellant has provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded polypeptide. Hyman et al. found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO1112 would be correlated with elevated levels of mRNA or polypeptide. Since Hyman et al. found that, at best, less than half of the amplified genes were overexpressed at the mRNA level, Hyman et al. supports the basis of the rejections that it is more likely than not that gene amplification *fails* to correlate with increased mRNA/polypeptide levels. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung or colon cancer.

At pp. 4-5 of the Appeal Brief, Appellant argues that, even if there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene amplified in cancer is still useful. Appellant refers to the Ashkenazi declaration and the Hanna and Mornin publication as evidence that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification and leads to a better determination of a suitable therapy. This has been fully considered but is not found to be persuasive for the following reasons. The Ashkenazi declaration under 37 CFR 1.132 filed 25 June 2004 is insufficient to overcome the rejection of claims 119-123 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons. First, the specification never suggests that gene amplification in the absence of polypeptide over-expression leads to better tumor classification and more suitable therapy determination. See p. 539 of the specification that states unequivocally that gene amplification is associated with over-expression of the gene product (e.g., polypeptide), indicating that the polypeptides are useful targets for therapeutic intervention in cancer and diagnostic determination of cancer. P. 539 also states that antibodies are useful therapeutics. Therefore, the Ashkenazi declaration and the Hanna and Mornin publication contradict the asserted utility in the specification. Furthermore, nowhere in the specification are suitable therapies disclosed for cancers in which PRO1112 polypeptides are over-expressed as opposed to cancer in which PRO1112 is not over-expressed. The determination of such clearly requires significant further research, thus evidencing that the asserted utility is not substantial.

At p. 5, second paragraph, of the Brief, Appellant argues that the sale of gene expression chips constitutes evidence that the research community believes that the information obtained from these chips is useful in that it is more likely than not that the information is informative of polypeptide levels. This has been fully considered but is not found to be persuasive for two reasons. First, evidence of commercial success, while probative as a secondary consideration of non-obviousness, has no bearing on the legal issue of utility and enablement. Second, gene chips speak to the issue of whether mRNA levels are predictive of polypeptide levels, which is no longer relevant to the instant rejections.

At the third to fifth paragraphs of p. 5 of the Appeal Brief, Appellant concludes that one skilled in the art would find it credible that the claimed PRO1112 antibodies have utility as markers for diagnosis of lung and colon tumors, and would know how to make and use such antibodies as diagnostic markers. This has been fully considered but is not found to be persuasive. To clarify, the utility rejection is based upon the failure of the asserted utility to be substantial; credibility has not been questioned. The specification asserts that PRO1112 antibodies are useful as markers for lung and colon cancer. Such is specific, and credible in that such is certainly possible. However, the asserted utility is not substantial since significant further research would be required *to reasonably* confirm the real-world use. The art directs the skilled artisan to such further testing by establishing that it is more likely than not that gene amplification fails to correlate with protein over-expression unless the protein is established as being beneficial to cell survival or growth. Since it was not known or disclosed if PRO1112

provides a selective growth or survival advantage to a cell, experimentation would have to be conducted to determine such. See Pennica et al., Konopka et al., Fleischhacker et al., Godbout et al., Hittelman, Li et al., Sen, and Hanna and Mornin.

Appellant's detailed arguments begin at the bottom of p. 5 of the appeal brief. Appellant begins with a review of the legal standard for utility, with which the examiner takes no issue.

Beginning at p. 9 of the Brief, Appellants review Example 170, and refer to the Goddard declaration as establishing that an amplification of at least 2-fold is significant and indicative of a cancer diagnostic marker. The Goddard declaration under 37 CFR 1.132 filed 25 June 2004 is insufficient to overcome the rejection of claims 119-123 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2.092 to 4,807 fold amplification in twelve out of fourteen colon cancer samples and 2.192 to 3.364 fold amplification in seven out of fourteen lung cancer samples is significant, and whether such data have any relevance to the claimed

subject matter, i.e., PRO1112 antibodies. The significance can be questioned based on the strength of opposing evidence. In the instant case, the data were not corrected for aneuploidy and the controls used were not matched, non-tumorous lung and colon samples but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al.). This art, as well as the Sen, Godbout et al., and Li et al. references cited above, constitute strong opposing evidence as to whether or not the claimed antibodies have utility and enablement based on a presumption of polypeptide overexpression in view of gene amplification data. Finally, while the Goddard declaration speaks to the utility and enablement of genes, it does not speak to whether or not the encoded polypeptides are also found at increased levels in cancerous tissues. Since the claims under examination are directed to antibodies (which only bind and detect polypeptide levels), not genes, this question is critical.

At p. 11 of the Brief, Appellant argues that the gene amplification was not due to aneuploidy. Appellant also points to the Ashkenazi declaration as showing that gene amplification is still useful for cancer diagnosis even if the determination includes chromosomal aneuploidy. Referring to Sen, Fleischhacker et al., and Hittelman, Appellant agrees that aneuploidy can be a feature of damaged tissue and may not invariably lead to cancer. However, Appellant reasons that PRO1112 is still useful in diagnosing pre-cancerous lesions or cancer itself. Appellant urges that the prior art is consistent with this view. This has been fully considered but is not found to be persuasive. The specification does not assert that the PRO1112 polypeptides or antibodies are useful as diagnostic markers for damaged epithelial tissues. The

specification clearly asserts that the markers are for cancer diagnosis and therapeutic drug development only. Therefore, Appellant's arguments are in contradiction to the asserted utility in the specification and, in fact, support the rejections.

Beginning at p. 12 of the Appeal Brief, Appellant argues that a *prima facie* case of lack of utility has not been established. Appellant urges that the proper legal standard is "more likely than not" rather than "necessarily." Appellant criticizes Pennica et al. as being limited to individual WISP genes, and that no general trends can be concluded therefrom. Appellant points to the correlation between WISP-1 gene amplification and polypeptide overexpression. At p. 13 of the Brief, Appellant takes issue with the Konopka et al. reference, again urging that Konopka et al. is limited to a single gene, and teach nothing regarding the correlation between gene amplification and protein expression levels in general. This has been fully considered but is not found to be persuasive. The instant application also presents data from a single gene at a time and makes conclusions about gene products from genomic DNA data. Pennica et al. constitutes evidence that it cannot be assumed that amplified genomic DNA for a single gene results in overexpressed gene product. Godbout et al. and Li et al. also provide evidence to this effect with respect to the general concept of whether or not gene amplification correlates with increased mRNA/polypeptide expression. Finally, Sen constitutes evidence that, in general, non-cancerous epithelial tissues are frequently aneuploid, and thus an increase in genomic DNA is not diagnostic of cancer.

At pp. 13-14 of the Brief, Appellant takes issue with the Godbout et al. reference. Appellant argues that it was never claimed that PRO1112 is similar to the DDX1 gene of

Godbout et al. Appellant urges that Godbout et al. evidences the good correlation between gene amplification and protein expression levels. Appellant argues that the examiner's requirement for structure/function data is not required for utility. This has been fully considered but is not found to be persuasive. As discussed above, the art indicates that *only* those amplified genes which confer a selective advantage on the cell is overexpressed in cancer cells. Godbout et al. (1998, J. Biol. Chem. 273(33):21161-8) state "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. ***Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified***." (emphasis added). The polypeptide encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. Contrary to Appellant's characterization of the reference, on page 21167, right column, first full paragraph, Godbout et al. state ***"It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell*** (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region

(GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." (emphasis added). There is no evidence in the instant application that PRO1112 confers any selective growth advantage to a cell, and thus it cannot be presumed that the PRO1112 polypeptide is overexpressed because the genomic DNA including the gene being studied is amplified.

At p. 14 of the Appeal Brief, Appellant criticizes Li et al. Appellant urges that Li et al. acknowledge that their results differed from those of Hyman et al. and Pollack et al., and note that the difference may be due to different methodologies. Appellants refer to the supplemental information accompanying the Li et al. article, enclosed with the Brief. Appellants urge that Li et al. used an amplification copy ratio of only 1.4, which is not significant according to the Goddard declaration, and that a copy number of at least 2 was necessary. This has been fully considered but is not found to be persuasive. First, it is noted that Hyman et al. also found that less than half of the amplified genes were overexpressed at the mRNA level, even though they only investigated genes in genomic DNA regions that were amplified at least 2-fold, and thus Hyman et al. supports the examiner's position. Furthermore, Li et al. did not limit their studies to genes that were amplified at less than 2-fold. In fact, the supplemental information indicates that some of the samples were required to bind with a probe requiring at least 2-fold amplification:

> Genes with copy number ratio > 1.40 (representing the upper 5% of the CGH ratios across all experiments) were considered to be overrepresented. A genomic fragment that contained six or more adjacent probes showing a copy number ratio > 1.40, or a region with at least three adjacent probes with a copy number ratio > 1.40 **and no less than one probe with a ratio > 2.0**, were considered to be amplicons. (emphasis added, from 1st page of supplemental material)

At pp. 14-16 of the Appeal Brief, Appellant argues that it is "more likely than not" for amplified genes to have increased mRNA and protein levels. Appellant refers to Orntoft et al., Hyman et al., and Pollack et al. as evidencing that, in general, gene amplification increases mRNA expression. This has been fully considered but is not found to be persuasive. Orntoft et al. could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract). It would appear that Appellant has provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded polypeptide. Hyman et al. found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO1112 would be correlated with elevated levels of mRNA, much less polypeptide. Since Hyman et al. found that less than half of the amplified genes were overexpressed at the mRNA level, Hyman et al. supports the basis of the rejections that it is more likely than not that gene amplification *fails* to correlate with increased mRNA/polypeptide levels. Pollack et al. is similarly limited to highly amplified genes

which were not evaluated by the method of the instant specification. Furthermore, it is interesting to note that Pollack et al. found correlations in their breast cancer samples, but referred to another investigative group that found very poor correlations in colon cancer samples. See bottom of right column of p. 12967 of Pollack et al. wherein they discuss Platzer et al. Also interesting is that Pollack et al. used a normal female leukocyte DNA control from a single donor rather than normal breast tissue (matched tissue control), whereas Platzer et al. compared colon cancer samples to normal colon epithelium. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung or colon cancer.

At p. 16 of the Appeal Brief, Appellant urges that the sale of gene expression chips to measure mRNA levels evidences that the research community believes that the information obtained from these chips is useful in that it is more likely than not that the information is informative of polypeptide levels. This has been fully considered but is not found to be persuasive for two reasons. First, evidence of commercial success, while probative as a secondary consideration of non-obviousness, has no bearing on the legal issues of utility and enablement. Second, gene expression chips speak to the issue of whether mRNA levels are predictive of polypeptide levels, which is no longer relevant to the instant rejections.

At the bottom of p. 16 of the Brief, Appellant argues that the examiner has disregarded the allegedly ample evidence by misinterpretation. Appellant urges that the publications evidence that it is more likely than not that gene amplification correlates well with protein over-expression, and that such would be accepted as reasonable and

credible by one in the art. Appellant urges that the "more likely than not" standard is lower than the "accurate" or "necessary" standard. Appellant urges that the examiner has provided no evidence or arguments as to why Appellant's assertion of over-expression would not be credible. This has been fully considered but is not found to be persuasive because it is inaccurate. The rejection discusses each publication and other piece of evidence brought forth on the record regarding this issue and has concluded, based on the preponderance of the totality of the evidence, that it is more likely than not that gene amplification fails to correlate with protein over-expression. Patentable utility must be credible, specific, and substantial. Credibility and specificity have not been questioned. However, the asserted utility is not substantial because it would require further research to reasonably confirm a real world use. The rejection is supported by several pieces of evidence that show that gene amplification cannot be assumed to correlate with protein overexpression. See Pennica et al., Konopka et al., Sen, Hittelman, Godbout et al., Li et al., Hanna and Mornin, and the Ashkenazi declaration. Since the priority filing date of June 1998, no evidence has been brought forth on the record as to whether or not the polypeptide level of PRO1112 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since the asserted utility for the claimed polypeptides is not in currently available form, and further experimentation is *required* to reasonably confirm the asserted real-world use, the asserted utility is not substantial.

At p. 17 of the Brief, Appellant argues that Hyman et al. conducted additional experiments on one of their genes, HOXB7, and found a clinical association between

HOXB7 amplification and poor prognosis. Appellant urges that Hyman et al. confirm that amplified genes have diagnostic utility. Appellant points to the final paragraph of Pollack et al. wherein it is stated that a substantial portion of the phenotypic uniqueness among patients' tumors may be traceable to variation in DNA copy numbers, and argues that this statement confirms that genes that are amplified are useful as markers and for prognostic uses. This has been fully considered but is not found to be persuasive. Hyman et al. and Pollack et al. relied on significant further research to identify a very small number of genes that had potential as cancer markers. For example, Hyman et al. identified 270 specific amplified genes, but only identified one, HOXB7, as being potentially associated with poor prognosis. Hyman et al. only suggested such in view of other research that had already linked HOXB7 to cancer. See second paragraph on p. 6244, wherein Hyman et al. refer to six other research papers regarding HOXB7 and cancer, including experiments wherein HOXB7 was transfected into normal cells and induced cell proliferation and tumorigenicity. Pollack et al.'s final paragraph contains several cautionary notes about their findings, including a specific statement at p. 12968 that "this finding cautions that elevated expression of an amplified gene cannot alone be considered strong independent evidence of a candidate oncogene's role in tumorigenesis….This highlights the importance of high-resolution mapping of amplicon boundaries and shape..on a large number of samples, in addition to functional studies." Thus, the art clearly directs the skilled artisan to further experimentation before identifying any amplified gene or its expression product as a diagnostic marker or a target for therapeutic intervention, clearly supporting the

rejection's findings that the asserted utility is not substantial.

Beginning at p. 17 of the Brief, Appellant argues that, even is a *prima facie* case of lack of utility has been established, it should be withdrawn based on the totality of the evidence. Appellant again draws attention to the Ashkenazi declaration, urging that gene amplification even without protein over-expression is useful in that it assists the clinician in tumor classification and selection of treatment modalities that are specific to the tumor, thus avoiding excess cost and side effects. This has been fully considered but is not found to be persuasive. The specification does not disclose such further testing of gene product overexpression. Therefore, the skilled artisan would have been required to do the testing to reasonably confirm whether or not the PRO1112 polypeptide is over-expressed. In view of such requirement, the products or services based on the claimed invention are not in "currently available" form for the public. Furthermore, the specification provides no assertion that the claimed PRO1112 polypeptides are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO1112. For example, neither the specification nor the prior art discloses an agent that targets PRO1112 that is useful for cancer therapy. This is also further experimentation that would have to be performed by the skilled artisan, indicating that the asserted utility is not substantial.

At p. 18 of the Brief, Appellant argues that the opinion of Dr. Ashkenazi is supported by the Hanna and Mornin reference. Appellant urges that the publication evidences that the HER-2/neu gene is over-expressed in breast cancers, and teaches

that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Appellant argues that the disclosed assay leads to a more accurate classification of the cancer and a more effective treatment of it. The examiner agrees. In fact, Hanna and Mornin support the rejection, in that Hanna and Mornin show that gene amplification does not reliably correlate with protein over-expression, and thus the level of protein expression must be tested empirically. The specification does not provide this further information, and thus the skilled artisan must perform additional experiments. Since the asserted utility for the claimed antibodies is not in currently available form, and requires further experimentation to reasonably confirm the suggested use, the asserted utility is not substantial. Finally, it is no small matter to go from information regarding protein expression levels in a tumor to designing a therapeutic regimen specific to the protein expression profile. In Hanna and Mornin, Herceptin was discussed as a drug specific to tumors expressing HER-2/neu. Herceptin had been known prior to the publication of Hanna and Mornin. No such drug is disclosed in the specification, nor in the prior art, regarding the PRO1112 polypeptide. Identifying a drug specific for PRO1112 would involve more than routine experimentation, as it would require a great amount of experimentation (e.g., screening agents for effects on PRO1112 polypeptide and on tumor), considering there is no guidance or working examples relative to such drugs in the specification or the prior art.

At p. 18, Appellant urge that the examiner has misread Hanna and Mornin, and quote from Hanna and Mornin that, in general, FISH and IHC correlates well. Appellant

urges that only a subset of tumors show discordant results. This has been fully considered but is not found to be persuasive. Hanna and Mornin do not appear to disclose the percentage of tumors having a correlation and those not having a correlation. However, Hanna and Mornin clearly caution the clinician not to assume that HER-2/neu protein is over-expressed based on gene amplification tests, since administering Herceptin to patients not over-expressing HER-2/neu was harmful. Thus, the art directs the skilled artisan to do the further experimentation on the expression levels of the protein.

At p. 18, last paragraph, Appellant argues that the specification demonstrates PRO1112 gene amplification in multiple lung and colon tumors and concludes that PRO1112 is a tumor associated gene like HER-2/neu. Appellant urges that gene amplification, in the majority of cases, influences mRNA and protein levels, allegedly based on the art. Appellant concludes that the skilled artisan would reasonably expect that PRO1112 protein is over-expressed in lung and colon tumors. This has been fully considered but is not found to be persuasive. The preponderance of the evidence clearly indicates that gene amplification cannot be assumed to correlate with protein overexpression. See Pennica et al., Konopka et al., Hittelman, Sen, Godbout et al., Li et al., Hanna and Mornin, and even the Ashkenazi declaration and the Hyman et al. article. The art directs the skilled artisan to perform further experiments to determine whether or not a protein is over-expressed in cancer tissue. Thus, since further experimentation is clearly required to reasonably confirm the asserted utility, the asserted utility is not substantial.

At p. 19 of the Brief, Appellant argues that the examiner improperly views the further testing described in the Ashkenazi declaration as further characterization of the PRO1112 protein itself. Appellant asserts that the experimentation described is only further characterization of the tumor, not the polypeptide. Appellant argues that the PRO1112 polypeptide is useful in tumor categorization, enabling the physician to select a treatment modality that holds the most promise for successful treatment of a patient. This has been fully considered but is not found to be persuasive. The tissue specific pattern of expression of a protein is definitely a feature of the protein itself. The determination of such is a form of characterizing the protein. Furthermore, no treatment modalities specific to PRO1112 have been disclosed in the specification or prior art. The identification of such would require significant further research, thus also indicating that the asserted utility is not substantial.

At p. 19 of the Brief, Appellant concludes by arguing that, based on the asserted utility for PRO1112 in lung and colon cancer diagnosis, the reduction to practice of the protein of SEQ ID NO: 207, the disclosure of protocols for making chimeric PRO polypeptides such as those claimed and for recombinant expression of PRO1112, the disclosure of protocols for making PRO1112 antibodies, and the gene amplification assay, the skilled artisan would know exactly how to make and use the claimed antibodies for diagnosis of lung cancers. Appellant urges that testing would have been routine and not undue. This has been fully considered but is not found to be persuasive. The rejection is supported by the preponderance of the evidence. Regarding the gene amplification assay itself, it is noted that the assay did not correct

for aneuploidy, which is a common feature of non-cancerous, damaged lung and colon epithelium (evidenced by Sen and Fleischhacker et al.). The specification does not assert a utility for PRO1112 as a biomarker for damaged, pre-cancerous tissue, and such is not a well-established utility. Gene amplification publications used matched tissue controls, unlike Appellant (Pennica et al., Godbout et al., Li et al.). Contrary to Appellant's assertions, the state of the art indicates that gene amplification is not generally associated with over-expression of the encoded gene product, as evidenced by Sen, Pennica et al., Godbout et al., Hyman et al., and Li et al. The declaration setting forth the expert opinion of Dr. Ashkenazi contradicts the assertion of utility in the specification, wherein the specification indicates that gene amplification is associated with protein over-expression but Dr. Ashkenazi indicates that this is not always the case. Hanna and Mornin provide evidence that the level of polypeptide expression must be tested empirically to determine whether or not the polypeptide can be used as a diagnostic marker for a cancer. The specification does not provide data as to whether or not the polypeptide level of PRO1112 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since significant further research would have been required of the skilled artisan to reasonably confirm that PRO1112 polypeptides are over-expressed in any cancer to the extent that they or their antibodies could be used as cancer diagnostic agents, the asserted utility is not substantial. Even more research would be required of the skilled artisan to determine if the claimed PRO1112 antibodies can be used as cancer therapeutics, since there is no evidence that PRO1112 plays a role in cancer formation

or progression such that inhibiting PRO1112 would result in effective cancer therapy. In the absence of information regarding whether or not PRO1112 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO1112 **polypeptides and antibodies** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the claimed antibodies. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an Appellant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

(12) Oral Hearing

At this time, it does not appear that Appellant has requested an oral hearing. However, if Appellant requests an oral hearing subsequent to the mailing of this examiner's answer, the examiner requests the opportunity to present oral arguments at the hearing.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Elizabeth C. Kemmerer, Ph.D./

Primary Examiner, Art Unit 1646

Conferees:

/Gary B. Nickol /

Supervisory Patent Examiner, Art Unit 1646

/Manjunath N. Rao, /

Supervisory Patent Examiner, Art Unit 1647